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Introduction of Planaria as a New Model for Multiple Sclerosis Research: Evidence from Behavioural Differences in Cuprizone Treated Planaria Exposed to Patterned Magnetic Fields

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Abstract

There has been a substantial history of correlative associations between subtle changes in geomagnetic intensity and the prevalence of multiple sclerosis. Several experiments have shown that rats in which experimental allergic encephalomyelitis had been induced respond to naturally-patterned weak magnetic fields. Exposures of only 6 min once per hour during the scotophase to a ~ 50 nT, 7 Hz magnetic field whose amplitude modulations simulated a sudden geomagnetic storm commencement markedly reduced both the behavioural symptoms and mononuclear cell infiltrations. In the present study planarian were exposed for only 6 min per day for three days to this same field pattern and intensities but with or without the presence of the demyelinating agent cuprizone. Behavioural analysis indicated a strong interaction after one day of exposure between cuprizone and field conditions for the numbers of "head whips" and an indicator of "unusual behaviours." The 6 min exposures to the patterned magnetic field on the second and third days eliminated the effects of cuprizone upon the numbers of head whips and related anomalous behaviours. General activity was not affected. The specificity of the simultaneous exposure to the magnetic field and cuprizone for normalizing the planaria is consistent with the results of rodent studies involving one model of multiple sclerosis and suggests that this paradigm might be useful for examining the potential mechanisms for the correlation between prevalence of MS and geomagnetic variables.

Keywords: Planarian; Geomagnetic intensity; Cuprizone; Multiple sclerosis; Demyelination; Weak intensity

Introduction

Of the commonly used animal models for demyelination, the cuprizone (CPZ) model allows for direct investigation of myelin damage and resulting repair. In rat models, cuprizone first binds copper ions, disrupts the function of the cytochrome complex, reduces the membrane potential in the mitochondria, and creates an oxidative stress and energy shortage [1,2]. This stress disturbs the normal functions of the endoplasmic reticulum in processing lipids and amino acids that contributes to oligodendrocyte degeneration and disintegration of the myelin sheath [3]. The damage then triggers an immune response including astrogliosis and subsequent micro gliosis to phagocytise the myelin debris [4,5]. Unlike human multiple sclerosis (MS), cuprizone induced models do not activate T and B cells. There has been no observable evidence of lymphocyte infiltration in damaged brain foci [3]. Cuprizone does not increase the permeability of the blood-brain barrier (BBB) which is often seen in MS which allows the auto-reactive T cells direct access to the CNS [3,6].

It has been suggested that differential intensity of the earth's magnetic field is a correlative environmental risk factor in developing MS. In an extensive epidemiological review, Sajedi and Abdollahi found a positive correlation between geographic latitude and reported prevalence of multiple sclerosis around the world [7]. A geographic (implicitly related to proportions of solar hours) is also central to the Vitamin D Hypothesis. However; when these authors compared the geographic latitude to the geomagnetic field strength of each study centre, they found a positive correlation between MS prevalence and geomagnetic field intensity, compared to geographic location alone. Time-varying magnetic fields generated by "cancelling" the background static field within the 50 nT range have previously been demonstrated to markedly attenuate Experimental Allergic Encephalomyelitis (EAE) in the Lewis rat [8-10]. Weaker, more complex fields have been reported to treat some MS cases in human beings [11].

The planarian flatworm has become popular for a multitude of human diseases due in part to their similarity to the human central nervous system. Physically, the planarian central nervous system is composed of a central cluster of ganglions with two ventral nerve cords with neurons and glial cells that resemble cytological structures in vertebrate nervous tissue [12]. Chemically, they possess neurotransmitters and associated receptors found in vertebrates including acetylcholine, catecholamines, GABA, and serotonin [13]. Perhaps the most exciting feature of these flatworms is their extensive ability to regenerate. Planaria possess an abundance of pluripotent stem cells (neoblasts) which give them the capability to fully regenerate all body parts including nervous tissue [14,15]. A planarian can be segmented into 279 pieces and each fragment will regenerate into a full worm [16]. All of these features have allowed researchers to study a variety of neurological disorders from addiction and withdrawal mechanisms to neurodegenerative disorders [17,18].

The current investigation was designed to examine the planarian as a possible model to understand the potential geomagnetic contribution to the prevalence for multiple sclerosis (MS). We reasoned that if the geomagnetic effect was not a confounding association, then the effects of experimentally manipulating a natural intensity magnetic field upon planarian behaviour should interact with a more well known chemical

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treatment. One of these agents with potential application is cuprizone which has been considered a demyelinating agent. Since planaria lack an adaptive immune system, this experiment was designed to affect the pluripotent stem cells of planaria [19]. We also planned to discern if magnetic fields that simulate a geomagnetic event could reduce behavioural symptoms in a cuprizone model as they did in prior studies which examined EAE in rats [8-10]. Those experiments had simulated a "sudden storm commencement" or "sudden impulse" as outlined by Mayaud which exhibited an average duration of about six minutes and intensity fluctuating between 50-100 nT [20]. These field parameters were similar to those used in past studies. The primary difference was the rats had been exposed multiple times during the dark cycle whereas the planaria were exposed only once daily [8-10].

Materials and Methods

Planaria and chemical compounds

Brown planaria (*Dugesia tigrina*) were acquired from Carolina Biological Supply (Burlington, North Carolina) and housed in group containers containing fresh spring water in darkness until use [21]. Cuprizone (bis-cyclohexanone-oxaldihydrazone) was acquired from Sigma-Aldrich and dissolved in ethanol in spring water to the desired concentration of 0.5% w/w cuprizone (35 μM), 0.1% ethanol. This concentration is within the range of doses for cuprizone demyelination in rats and mice [22,23].

Patterned magnetic fields

The magnetic field was generated using a digital to analog converter (DAC) and a coil with dimensions of 38 cm x 33 cm x 27 cm which was wrapped with 305 metres of 30 AWG wire as described by Murugan et al. [24]. A custom constructed digital-to-analogue converter transformed a series of 5,071 numbers each between 1 and 256 which were equivalent to voltages between -5 and +5 V. The numbers were contained within Complex Software formatted for an XT personal computer. The point duration of each voltage (number value) was 69 milliseconds such that one cycle completed through a series of numbers (1-256) formed a temporal pattern. The magnetic field pattern used simulated the typical onset of a geomagnetic storm (a sudden storm commencement or "sudden impulse") whose duration was about 6 min. A diagram of the shape has been published several times.

Essentially it is a fundamental 7 Hz square wave containing two envelopes of increasing and decreasing amplitude modulations around 36 mHz and 71 mHz. The intensity fluctuated between 40 and 100 nT according to a power meter. A MEDA magnetometer verified the displacement in the x-axis only (the direction of the field from the coil) of about 40 nT. It is important to emphasize that when the field was generated by the equipment the static component of the x-axis of the static geomagnetic field decreased by a maximum of 40 nT during the peak components of the pattern. In other words the pattern was created within the increment between the diminished component of the geomagnetic field and the normal values for the field. We have found that this cancellation of a component of the local static field within which the experimentally generated temporally patterned field is then replaced produces the most robust biological and behavioural effects.

The exposure area for the planarian was 1.4 m from the center of the coil in order to obtain the required intensity to simulate that which produced the maximum reduction of EAE in rats. The orientation of the coil with respect to the earth's magnetic field was about 14° east of due magnetic north. The inclination was 71° and the resultant field was 49,080 nT (± 5 nT). The average static x, y, and z components (± 5 nT) were 14, 692, 3,857, and 47, 673, respectively. The surface upon which the containers for the planarian were placed was directly on the smoothed bedrock in the basement of the building.

Experimental Procedure

To establish a dosage curve, planaria (N=60) were divided into six treatment groups: a water control, a 0.1% ethanol control, and 0.1%, 0.2%, 0.5% or 0.8% cuprizone solution groups. Therefore, there were a total of 10 planaria per condition. Planaria were then placed into 1.5 mL plastic conical centrifuge tubes (Fisherbrand with dimensions of 10.8 x 40.6 mm). Each tube contained one worm and 1 mL of fluid. It was held upright in a plastic rack throughout the experiment. Behaviours were monitored daily after which the solutions were replaced for a total of three days.

To assess the effects of magnetic field treatment on cuprizone treated planaria, over three trials (weeks), on three separate days, planaria (N=60) were divided into four treatment groups: a water control, cuprizone treated, magnetic field treated water control and a cuprizone with magnetic field treatment group. Therefore, there were a total of 15 planaria per condition. Planaria were then placed into 1.5 mL plastic conical centrifuge tubes (Fisherbrand with dimensions of 10.8 x 40.6 mm). Each tube contained one worm and 1 mL of fluid and were held upright in a plastic rack throughout the experiment. On the first day of each trial, planaria were placed into their individual tubes along with 1 mL of either 0.5% cuprizone solution or spring water [25]. Each subsequent day, the planaria were exposed to the magnetic field or a sham condition (no field). Their behaviours were monitored for five minutes.

Behavioural paradigm

Planaria were placed in a small petri dish containing 3 mL of spring water on top of 0.5 cm grid paper. Over a five minute observation period, the numbers of gridlines crossed (known as the planarian locomotor velocity or pLMV) and frequency of atypical behaviours including head-whips, tail-twists, squirming and corkscrews were recorded as described by Raffa and Valdez [18].

Statistical analyses

The basic design was a four way analysis of variance with three between levels (magnetic field, cuprizone, replicate or weeks) and one within subject (trials). Statistical tests included multiple level analysis of variance, one-way analysis of variance and *post-hoc* Tukey tests to discriminate group differences. The mean of the three trials for each behavioural measure was analyzed for main effect comparisons. All statistical analyses were performed using PC IBM SPSS Statistics Version 20.

Results

The grand means and standard deviations (in parentheses) for behaviours during the dosage curve experiment were as follows: squares traversed: 58.5 (15.4), head whips: 31.0 (9.3), tail twists: 2.2 (1.6). cork screw: 1.3 (1.3), and squirming: 0.61 (0.75). Two way analysis of variance, as a function of treatment group and day, revealed strong group and day effects for the numbers of headwhips during the observation period. On day one, planaria displayed a lower amount of headwhips [$F(2,177) = 3.34$, $p=0.038$], while at days two and three were no statistically significant differences ($p>0.05$). Analysis of variance using only data from these two days demonstrated a significant difference between treatment groups for number of headwhips [F

(5,117) = 30.7, p<0.001]. These results can be seen in (Figure 1) with SEMs to demonstrate significance. A *post-hoc* Tukey test confirmed that all cuprizone treated groups varied significantly from the water control (p<0.05). Also, the ethanol control group displayed less headwhips than the 0.5% and 0.8% cuprizone groups. For this reason, the 0.5% concentration was used for further experiments to minimize the effect of the solvent.

The grand means and standard deviations (in parentheses) for the various measures were: squares traversed: 64.0 (11.6), head whips: 27.3 (7.9), tail twists: 0.25 (0.38), cork screws: 0.37 (0.47), and squirming: 0.15 (0.23). Four way analyses of variance as a function of field condition, cuprizone, replication and trial (within subject) for the five measures separately revealed multiple main effects for the three between subject measures. The planarian exposed to the magnetic field displayed significantly fewer headwhips [F (1,48)=20.15, p<0.001] compared to the no field conditions. There were no statistically significant treatment differences for any of the other four measures. On the other hand the planarian exposed to the cuprizone solution displayed significantly (all dfs=1,48) more headwhips [F=30.71], more squares traversed [F=6.69] more tailtwists [F=12.25], more corkscrews [F (8.16) and more squirming [F=20.63] than the comparison groups. The gross influence of cuprizone upon numbers of squares traversed is shown in (Figure 2). Standard errors of the mean (SEMs) are indicated to help demonstrate statistically significant differences between groups (treatments). There were statistically significant (all dfs=2,48) differences for all measures (except squirming) between the replicates, that is over the three separate weeks. *Post hoc* analyses

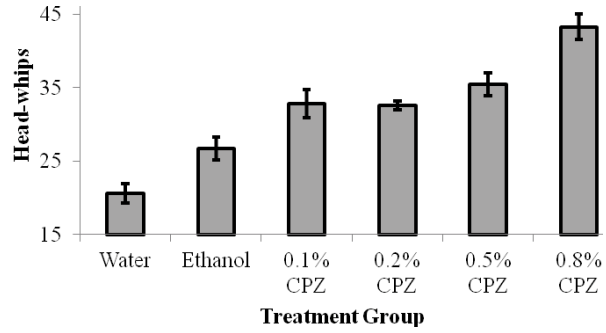

Figure 1: Number of head-whips during five minute observation period for varying concentrations of cuprizone. Results are displayed as Mean ± SEM.

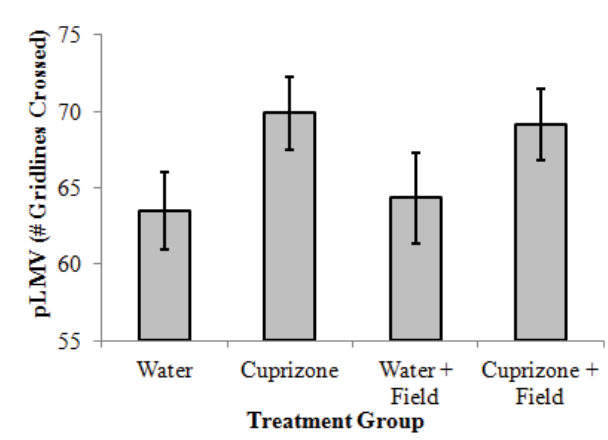

Figure 2: Mean planarian locomotor velocity (pLMV) during five minute observation period after field treatment. Results are displayed as Mean ± SEM.

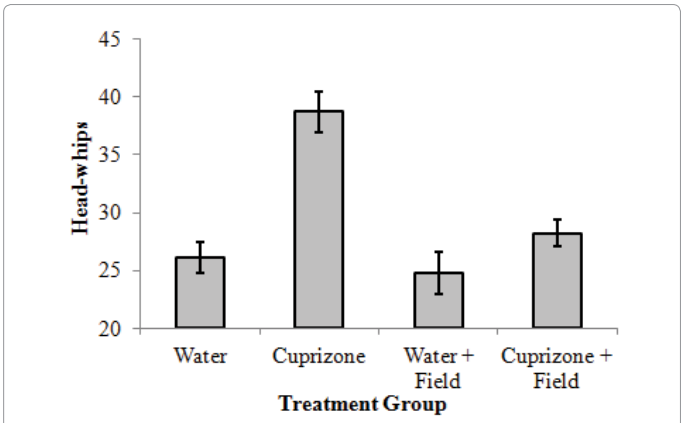

Figure 3: Number of head-whips during five minute observation period after field treatment. Results are displayed as Mean ± SEM.

indicated the planarian in the second block exhibited generally fewer responses for all behavioural domains.

Perhaps the most relevant result was the *interactions* between the simultaneous treatment by the cuprizone and the weak magnetic fields designed to simulate a sudden geomagnetic storm commencement or "sudden impulse." Analysis of variance indicated statistically significant interactions (all dfs=1,48) between cuprizone and magnetic field treatments for numbers of head whips [F=9.84], twists [F=8.03] and corkscrews [F=9.88]. The significant interactions were not apparent for either the numbers of squares traversed or squirming. The typical pattern (as indicated by head whips) of these interactions is shown in (Figure 3). Because there was a statistically significant interaction with trials (days) and the *post-hoc* analysis indicated that the major source of the interaction was for the second and third days of treatment, the means and dispersion measures reflect only those two days. The effects of the cuprizone upon the numbers of headwhips were eliminated if the planarian were simultaneously exposed for 3 days, 6 min per day to the magnetic field pattern.

Discussion

The results of these experiments indicated that brief exposures to a pharmacological treatment that may have relevance to processes contributing to myelinization and a complex amplitude-modulated weak (50 nT) magnetic field based upon a 7 Hz square wave fundamental pattern can produce specific and differential effects upon planarian behaviour. Whereas the cuprizone clearly affected gross movement behaviours as well as the qualitative patterns in which planarian engage, the effects of brief 6 min daily exposures to the magnetic field pattern only affected specific qualitative behaviours. Among the most robust was the numbers of head-whips which were not affected by the magnetic field only. The statistically significant main effect was confounded by the statistically significant interaction between curpizone and magnetic field treatments. However when the planaria were exposed to both treatments (Figure 2) the numbers of head-whips were reduced to control (water only) values.

These results suggest that the magnetic field pattern, even though the intensity was 50 nT and was presented for only 6 min, may have involved the same biochemical processes through which cuprizone mediates its effects. That weak magnetic fields can interact with pharmacological agents to ameliorate or exacerbate their effects has been shown by several researchers [26]. Recently Karbowski et al. showed that the relationship between molecular pathways related to

receptor-ligand binding and electromagnetic resonance patterns could involve the coherent organization of de-localized electrons as predicted by Cosic's Molecular Resonance Recognition model [27,28].

Although 50 nT (0.5 mG) might be considered minimal (and within the range of background 60 Hz power values in many habitats) changes within this range of intensity by diminishing the static geomagnetic field (rather than superimposing the experimental field) for more protracted periods has been shown to increase the rate of asexual reproduction (fission) in planarian by Novikov et al [29]. From a biophysical perspective the energy associated with this magnetic field strength within the volume (~ 10^{-11} m^3) according to the traditional relationship of $E=B^2 \cdot (2\mu)^{-1}$ m^3 where B is the field strength, μ is magnetic permeability and m^3 is volume would be about 10^{-20} J. This is within the range of energy involved with sequestering ligands as well as the quantity associated with the distance between potassium ions that contribute significantly to the resting membrane potential of the plasma membrane [30]. If the Cosic model is applicable, then once the energies for the applied and intraorganism conditions are matched, the critical determinant is the temporal pattern for the congruent "information". We reiterate that our fields were created by diminishing the static geomagnetic field and generating the experimental pattern within this alteration.

The observation that the synergistic amelioration of the curpizone effect on head whips (and related behaviours) occurred after the first exposure would also suggest that at least 24 hr is required for a process to emerge that would facilitate the drug-magnetic field interaction. A single exposure of 6 min to a patterned magnetic field with which there would be energetic equivalents induced within the planarian is well within the physiological time range to produce profound changes in cellular systems. For example to produce long-term potentiation (LTP) in hippocampal slices from the rodent brain a stimulation for only about 0.5 s at 100 to 400 Hz is required [31]. LTP is considered the primary mechanism by which experience is represented within neuronal arrays through alterations in protein sequences and depositions as (primarily) dendritic spines [32]. In other studies LTP, assuming the pattern of the electrical or electromagnetic sequences are appropriate, requires less than 6 min to produce changes that are maintained for days to years [33].

We are pursuing the concept that the cuprizone will produce a demyelination-like alteration in planarian that could be manifested in a variety of behavioural indicators. By understanding this process and how the applied magnetic field reduced specific components of this process, perhaps alternative treatments could be developed for patients who exhibit MS. Cook and Persinger showed remarkable diminishment of EAE in rats exposed to this same pattern of 6 min, intermittent stimulation [8]. In a single case study we exposed (whole-body) a middle-aged woman diagnosed with MS who was displaying moderately severe impairment to the same pattern and intensity while she was sleeping [34]. Before the treatment was terminated by request, she reported conspicuous reduction of the weakness and paraesthesia of the left side of her body.

The question then becomes why do we see these behavioural changes in planaria and not vertebrates? One plausible explanation is the mechanism for action of cuprizone itself. Cuprizone does not penetrate the blood-brain barrier (BBB) as it is not detected in brain tissue of treated animals [3]. Planaria on the other hand do not possess a BBB. Therefore, cuprizone would enter freely into nervous tissue, perhaps enhancing its chelating effect [35]. These structural differences between species may explain why behavioural changes are observed more easily in the planarian model of cuprizone demyelination than in past studies. Given the potential for periodic or transient reduction of the efficacy of the BBB in patients who are prone to or develop MS, the cuprizone model might still be applicable.

Although at this point we cannot say for certain which cellular and molecular processes are underlying these distinct changes we can hypothesize that the cuprizone invokes the same damage in planaria as rat models by causing increased oxidative stress and apoptosis of oligodendrocyte equivalents. This results in damage to the myelin and gliosis. This damage could then be halted by the effect of the patterned magnetic field. However, unlike past hypotheses suggesting it had an effect on the immune regulation in rats, we propose instead it acts to promote regenerative processes which are exacerbated in planaria due to the large number of pluripotent stem cells they possess. These observations suggest that the planarian cuprizone model may offer new insights into remyelination in multiple sclerosis due to their easily classifiable behaviours and extensive network of stem cells. Future histological, regenerative and molecular analyses may verify planaria as a superb test animal for multiple sclerosis treatments.

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